

WHAT IS CLAIMED IS:

1. A method of identifying an agent useful in treatment of a neurodegenerative disease, said method comprising:

(a) assaying for capacitative calcium entry (CCE) activity in cells treated with an agent;

(b) assaying for CCE activity in cells untreated with said agent; and

(c) comparing the CCE activities of (a) and (b) to determine whether said agent potentiates CCE activity in said cells treated with said agent, thereby identifying an agent useful in treatment of a neurodegenerative disease.

2. The method of claim 1, wherein said cells have a neurodegenerative disease-linked mutation.

3. The method of claim 2, wherein said neurodegenerative disease-linked mutation is a mutation causative of a neurodegenerative disease selected from Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis.

4. The method of claim 1, wherein said cells express an Alzheimer's disease-linked presenilin mutation.

5. The method of claim 1, wherein said cells contain an amyloid  $\beta$ -protein precursor (APP) mutant.

6. The method of claim 1, wherein said cells contain an apolipoprotein E (APOE) mutant.

7. The method of claim 1, wherein said neurodegenerative disease is selected from Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis.

8. The method of claim 7, wherein said agent is useful in treatment of Alzheimer's disease and inhibits the CCE-reducing activity of the Alzheimer's disease-linked mutation.

9. The method of claim 1, further comprising:

(d) assaying for CCE activity in cells treated with said agent, wherein said cells overexpress a transient receptor potential protein (TRP);

(e) assaying for CCE activity in cells treated with said agent, wherein said cells do not overexpress a TRP; and

(f) comparing the CCE activities of (d) and (e) to determine whether said agent potentiates CCE activity in said cells that overexpress a TRP.

10. A method of identifying an agent which inhibits capacitative calcium entry (CCE)-linked  $\gamma$ -secretase activity, said method comprising:

(a) assaying for CCE activity in cells treated with an agent;

(b) assaying for CCE activity in cells untreated with said agent;

and

(c) comparing the CCE activities of (a) and (b) to determine whether said agent increases CCE activity in said cells treated with said agent, thereby identifying an agent which inhibits  $\gamma$ -secretase activity.

11. The method of claim 10, wherein said cells express an Alzheimer's disease-linked mutation.

12. The method of claim 10, wherein said cells express an Alzheimer's disease-linked presenilin mutation.

13. The method of claim 10, wherein said cells contain an amyloid  $\beta$ -protein precursor (APP) mutation.

14. The method of claim 10, wherein said cells contain an apolipoprotein E (APOE) mutation.

15. The method of claim 10, wherein said agent useful in treatment of AD inhibits the CCE-reducing activity of the Alzheimer's disease-linked presenilin mutation.

16. The method of claim 10, further comprising:

(d) assaying for CCE activity in cells treated with said agent, wherein said cells overexpress a transient receptor potential protein (TRP);

(e) assaying for CCE activity in cells treated with said agent, wherein said cells do not overexpress a TRP; and

(f) comparing the CCE activities of (d) and (e) to determine whether said agent potentiates CCE activity in said cells that overexpress a TRP.

17. A method of treatment of a neurodegenerative disease in a subject, said method comprising: administering to said subject a pharmaceutically effective amount of an agent capable of potentiating capacitative calcium entry (CCE) activity in said subject.

18. The method of claim 17, wherein said neurodegenerative disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis.

19. The method of claim 18, wherein said neurodegenerative disease is Alzheimer's disease.

20. The method of claim 19, wherein said subject expresses a Alzheimer's disease-linked presenilin mutation.

21. The method of claim 20, wherein said agent inhibits the CCE-reducing activity of the Alzheimer's disease-linked presenilin mutation in said subject.

22. The method of claim 19, wherein said agent inhibits  $\gamma$ -secretase activity in said subject.

23. A method of identifying a transient receptor potential protein (TRP) involved in increasing capacitative calcium entry (CCE) activity, said method comprising:

- (a) providing cells which contain a presenilin mutation;
- (b) overexpressing a TRP to be tested in said cells; and
- (c) determining whether overexpression of said TRP increases CCE activity in said cells.

24. A method of identifying cellular components involved in capacitative calcium entry (CCE) inhibition, said method comprising:

- (a) incubating cellular protein(s) and SKF96365; and
- (b) characterizing and identifying the cellular protein(s) bound to said SKF96365.

25. A method of identifying an agent that reduces the ratio of amyloid  $\beta$  peptide A $\beta$ 42 to total amyloid  $\beta$  protein, reduces amyloid  $\beta$  peptide A $\beta$ 42

levels, or reduces the production of amyloid  $\beta$  peptide A $\beta$ 42 in a cell or extracellular medium, comprising:

- (a) assaying for capacitative calcium entry (CCE) activity in cells treated with an agent;
- (b) assaying for CCE activity in cells untreated with said agent;
- (c) comparing the CCE activities of (a) and (b) to determine whether said agent potentiates CCE activity in cells treated with said agent, thereby identifying an agent that reduces the ratio of amyloid  $\beta$  peptide A $\beta$ 42 to total amyloid  $\beta$  protein, reduces amyloid  $\beta$  peptide A $\beta$ 42 levels, or reduces the production of amyloid  $\beta$  peptide A $\beta$ 42 in a cell or extracellular medium.

26. The method of claim 25, wherein the cells comprise nucleic acid encoding an Alzheimer's disease-linked mutation.

27. The method of claim 25, wherein the cells comprise nucleic acid encoding a mutant presenilin.

28. The method of claim 25, wherein the cells comprise nucleic acid encoding a mutant amyloid  $\beta$  protein precursor.

29. A method of identifying an agent that reduces the ratio of amyloid  $\beta$  peptide A $\beta$ 42 to total amyloid  $\beta$  protein, reduces amyloid  $\beta$  peptide A $\beta$ 42 levels, or reduces the production of amyloid  $\beta$  peptide A $\beta$ 42 in a cell or extracellular medium, comprising:

- (a) assaying for transient receptor potential protein (TRP) activity in cells treated with an agent;
- (b) assaying for TRP activity in cells untreated with said agent;
- (c) comparing the TRP activities in (a) and (b) to determine whether said agent potentiates TRP activity in cells treated with said agent,

thereby identifying an agent that reduces the ratio of amyloid  $\beta$  peptide A $\beta$ 42 to total amyloid  $\beta$  protein, reduces amyloid  $\beta$  peptide A $\beta$ 42 levels, or reduces the production of amyloid  $\beta$  peptide A $\beta$ 42 in a cell or extracellular medium.

30. A method of identifying a candidate agent useful in treatment of a neurodegenerative disease, comprising:

- (a) assaying for transient receptor potential protein (TRP) activity in cells treated with an agent;
- (b) assaying for TRP activity in cells untreated with said agent;
- (c) comparing the TRP activities of (a) and (b) to determine whether said agent potentiates TRP activity in cells treated with said agent, thereby identifying a candidate agent useful in treatment of a neurodegenerative disease.

31. A method of reducing the ratio of amyloid  $\beta$  peptide A $\beta$ 42 to total amyloid  $\beta$  protein, reducing amyloid  $\beta$  peptide A $\beta$ 42 levels, or reducing the production of amyloid  $\beta$  peptide A $\beta$ 42 in a cell or extracellular medium, comprising administering to said cell or extracellular medium an agent that potentiates CCE activity in cells, thereby reducing the ratio of amyloid  $\beta$  peptide A $\beta$ 42 to total amyloid  $\beta$  protein, reducing amyloid  $\beta$  peptide A $\beta$ 42 levels, or reducing the production of amyloid  $\beta$  peptide A $\beta$ 42 in said cell or extracellular medium.

32. A method of reducing amyloid  $\beta$  peptide A $\beta$ 42 levels in a cell or extracellular medium, comprising administering to said cell or extracellular medium an agent that potentiates CCE activity in cells, thereby reducing amyloid  $\beta$  peptide A $\beta$ 42 levels in said cell or extracellular medium.

33. A method of reducing the production of amyloid  $\beta$  peptide A $\beta$ 42 in a cell or extracellular medium, comprising administering to said cell or extracellular medium an agent that potentiates CCE activity in cells, thereby reducing the production of amyloid  $\beta$  peptide A $\beta$ 42 in said cell or extracellular medium.

34. A method of treating a neurodegenerative disease in a subject, comprising administering to the subject a pharmaceutically effective amount of an agonist of a store-operated calcium channel.

35. A method of treating a neurodegenerative disease in a subject, comprising administering to the subject a pharmaceutically effective amount of an agonist of a transient receptor potential protein (TRP).

36. A method of treating a neurodegenerative disease in a subject, comprising administering to the subject a pharmaceutically effective amount of an agent that increases the level of transient receptor potential protein (TRP) in the subject.

37. A method of reducing the ratio of amyloid  $\beta$  peptide A $\beta$ 42 to total amyloid  $\beta$  protein, reducing amyloid  $\beta$  peptide A $\beta$ 42 levels, or reducing the production of amyloid  $\beta$  peptide A $\beta$ 42 in a cell or extracellular medium, comprising administering to said cell or extracellular medium an agonist of a transient receptor potential protein (TRP), thereby reducing the ratio of amyloid  $\beta$  peptide A $\beta$ 42 to total amyloid  $\beta$  protein, reducing amyloid  $\beta$  peptide A $\beta$ 42 levels, or reducing the production of amyloid  $\beta$  peptide A $\beta$ 42 in said cell or extracellular medium.

38. A method of reducing the ratio of amyloid  $\beta$  peptide A $\beta$ 42 to total amyloid  $\beta$  protein, reducing amyloid  $\beta$  peptide A $\beta$ 42 levels, or reducing the production of amyloid  $\beta$  peptide A $\beta$ 42 in a cell or extracellular medium, comprising administering to said cell or extracellular medium an agent that regulates expression of a transient receptor potential protein (TRP), thereby reducing the ratio of amyloid  $\beta$  peptide A $\beta$ 42 to total amyloid  $\beta$  protein, reducing amyloid  $\beta$  peptide A $\beta$ 42 levels, or reducing the production of amyloid  $\beta$  peptide A $\beta$ 42 in said cell or extracellular medium.

39. A method of reducing the ratio of amyloid  $\beta$  peptide A $\beta$ 42 to total amyloid  $\beta$  protein, reducing amyloid  $\beta$  peptide A $\beta$ 42 levels, or reducing the production of amyloid  $\beta$  peptide A $\beta$ 42 in a cell or extracellular medium, comprising administering to said cell or extracellular medium an agent that regulates cellular maturation of a transient receptor potential protein (TRP), thereby reducing the ratio of amyloid  $\beta$  peptide A $\beta$ 42 to total amyloid  $\beta$  protein, reducing amyloid  $\beta$  peptide A $\beta$ 42 levels, or reducing the production of amyloid  $\beta$  peptide A $\beta$ 42 in said cell or extracellular medium.

40. A method of reducing the ratio of amyloid  $\beta$  peptide A $\beta$ 42 to total amyloid  $\beta$  protein, reducing amyloid  $\beta$  peptide A $\beta$ 42 levels, or reducing the production of amyloid  $\beta$  peptide A $\beta$ 42 in a cell or extracellular medium, comprising increasing the level of transient receptor potential protein (TRP) in said cell or extracellular medium, thereby reducing the ratio of amyloid  $\beta$  peptide A $\beta$ 42 to total amyloid  $\beta$  protein, reducing amyloid  $\beta$  peptide A $\beta$ 42 levels, or reducing the production of amyloid  $\beta$  peptide A $\beta$ 42 in said cell or extracellular medium.

41. A method of identifying an agent useful in treatment of a neurodegenerative disease, said method comprising:



(a) assaying for capacitative calcium entry (CCE) activity in cells treated with an agent, wherein the cells overexpress a transient receptor potential protein (TRP);

(b) assaying for CCE activity in cells treated with said agent, wherein the cells do not overexpress a TRP; and

(c) comparing the CCE activities of (a) and (b) to determine whether said agent potentiates CCE activity in the cells that overexpress a TRP.

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